

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
14 July 2005 (14.07.2005)

PCT

(10) International Publication Number  
**WO 2005/063770 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 493/04**

PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,  
ZW.

(21) International Application Number:  
PCT/EP2004/053692

(22) International Filing Date:  
23 December 2004 (23.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(30) Priority Data:

03104949.7 23 December 2003 (23.12.2003) EP  
60/568,183 4 May 2004 (04.05.2004) US

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations* AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *of inventorship (Rule 4.17(iv)) for US only*

(71) Applicant (*for all designated States except US*): **TI-BOTEC PHARMACEUTICALS LTD.** [IE/IE]; Little Island, Co Cork (IE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **GOYVAERTS, Nicolaas, Martha, Felix** [BE/BE]; Welvaartstraat 69, B-2590 Berlaar (BE). **WIGERINCK, Piet, Tom, Bert, Paul** [BE/BE]; Kardinaal Cardijnstraat 29, B-2840 Terhagen (BE). **ZINSER, Hartmut, Burghard** [DE/CH]; J.J. Wepferstrasse 5, CH-8200 Schaffhausen (CH). **EBERT, Birgit, M.** [DE/CH]; Hochstrasse 311, CH-8200 Schaffhausen (CH).

(74) Agent: **DAELEMANS, Frank**; Tibotec-Virco Comm. VA, Generaal De Wittelaan L 11B 3, B-2800 Mechelen (BE).

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: PROCESS FOR THE PREPARATION OF (3R,3aS,6aR)-HEXAHYDROFURO [2,3-B] FURAN-3-YL (1S,2R)-3-[[4-AMINOPHENYL] SULFONYL] (ISOBUTYL) AMINO]-1-BENZYL-2-HYDROXYPROPYLCARBAMATE

(57) Abstract: The present invention relates to a process for the preparation of (3R,3aS,6aR)-hexahydrofuro [2,3-b] furan-3-yl (1S,2R)-3-[[4-aminophenyl] sulfonyl] (isobutyl) amino]-1-benzyl-2-hydroxypropylcarbamate as well as intermediates for use in said process. More in particular the invention relates to processes for the preparation of (3R,3aS,6aR)-hexahydrofuro [2,3-b] furan-3-yl (1S,2R)-3-[[4-aminophenyl] sulfonyl] (isobutyl) amino]-1-benzyl-2-hydroxypropylcarbamate which make use of 4-amino-N ((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-(isobutyl)benzene sulfonamide intermediate, and to processes amenable to industrial scaling up. (3R,3aS,6aR)-hexahydrofuro [2,3-b] furan-3-yl (1S,2R)-3-[[4-aminophenyl] sulfonyl] (isobutyl) amino]-1-benzyl-2-hydroxypropylcarbamate is particularly useful as HIV protease inhibitors.

WO 2005/063770 A1